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SUBJECT

Production of Alkaloids at Arzneimittelwerk
Dresden

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1. Morphine Alkaloids

a. Codeine

The Arzneimittelwerk-Dresden (A.W.D.) obtained crude opium (extracted from poppy sources) from a plant in Reichenberg-Niederlausitz. This crude opium had a purity of about 75 percent. The A.W.D. produced pure morphine from the crude opium by repeated recrystallization through a morphine salt. The morphine was then methylated to codeine. A.W.D. facilities produced approximately 20-30 kilograms of codeine a month.

b. Dihydrocodeine (Dehacodin, Paracodin)

A.W.D. produced this product from codeine by the following method:

- 1) Five hundred (500) grams of purified codeine, 50 grams of Raney nickel, and 800 cc. of anhydrous dioxane were placed in a five-liter autoclave and heated, with stirring or shaking, to 100-110°C. at a constant hydrogen pressure of 25 atmospheres for three to five hours. The reaction solution was cooled and decanted from the catalyst, and the residue completely removed from the finely divided nickel by filtration. The oily liquid obtained was golden yellow in color. The catalyst could be re-used at least four times without treatment.
- 2) A hot, filtered solution of 200 grams of tartaric acid, in four to five liters of anhydrous dioxane, was added with rapid stirring to the oily liquid. This procedure immediately yielded a viscous mass which changed to a voluminous, finely-crystallized form after being warmed for a brief period. These crystals were heated under reflux with two to three liters of methyl alcohol for 30 minutes. The liquid clouded after a period of time and the bitartrate of dihydrocodeine precipitated in a compact, crystalline form. This product satisfied the quality standards required by the control specifications; it melted at 100-100°C. and was 99.5-100 percent pure. A yield of 70-80 percent was obtained.

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- c. Dihydrocodeinone (Dioclid), Dihydro-hydroxycodeinone (Eukodal),
and Dihydromorphinone (Maudin)

Preliminary test procedures for the production of these products were underway in 1953, but none had been decided upon.

2. Solanaceous Alkaloids

a. Atropine and Hyoscyamine

- 1) ASD prepared hyoscyamine and atropine by extraction of Radix belladonnae with methyl alcohol. The pure alkaloid base-mixture was obtained by repeated crystallization from the concentrated extract and heating with charcoal. This product, containing about 60 percent atropine and 40 percent hyoscyamine, was sold as "Bellatotal" in tablet and suppository form.

b. Atropine Methyl Nitrate (Eumydrin)

- 1) Laboratory-scale production of atropine methyl nitrate was used at ASD in order to control the reactions carefully and avoid losses. The atropine base was prepared by dissolving 250 grams of atropine sulfate in about 350 cc. of water and precipitating the atropine by the addition, with stirring, of 330 cc. of 10 percent ammonium hydroxide. The precipitate was filtered, washed thoroughly with water (in which it was soluble 1:500) and dried in an oven at 60-70°C. The yield was 171.5 grams (32.4 percent) with a melting point of 117°C. The time required for this step was one hour.
- 2) The 171.5 grams of atropine were dissolved in 500 cc. of methyl alcohol, filtered, and treated with 3000 grams of freshly prepared methyl bromide. After the reaction mixture was allowed to stand in a cool place for a brief period, the atropine methyl bromide crystallized. The precipitated crystals were filtered off, washed with anhydrous ether, and allowed to dry in the oven at 100°C. A batch of crystals obtained from the mother liquor was treated in the same manner. The yield was 205 grams (25 percent) with a melting point of 221-224°C. The time required for the preparation of fresh methyl bromide was eight hours and for the atropine methyl bromide, three hours.
- 3) The 205 grams of atropine methyl bromide were dissolved in 10 volumes of water, filtered, and treated in separate portions with an equal amount of silver nitrate (90.5 grams in 910 grams of water). It was important at this stage to avoid adding an excess of silver nitrate and to filter off the precipitated silver bromide in order to note the last precipitation stages of the silver nitrate addition. The liquid was finally filtered from the silver bromide which was then washed with water. The clear filtrate was evaporated at a temperature not above 70°C, and the colorless or gray-brown oily residue was dissolved in a 3:1 mixture of acetone-alcohol. About 2500 cc. of this solvent were required. After gentle warming, and addition of charcoal, if the solution was brownish, the solution was filtered. Ether was added to the filtrate until a milky precipitation occurred. After the mixture was allowed to stand in a cool place, the atropine methyl nitrate precipitated in fine needles. The product was filtered off, washed several times with dry ether and dried at 70°C. for about one hour. The precipitate obtained by further addition of ether to the mother liquor was treated similarly. The yield was 166 grams (35.7 percent) with a melting point of 162.2-167.7°C. (with decomposition). This product was a white, microcrystalline powder, easily soluble in chloroform and ether. The time required for the

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preparation of the atropine methyl nitrate was eight hours. Atropine methyl nitrate was sold in a package containing 10-0.001 gram tablets.

c. Scopolamine

- 1) At the beginning of 1953 it was decided to widen the A.D alkaloid production to include scopolamine. This production was to utilize folia Datura metel. The organic solvent method customarily used could not be employed because of the simultaneous extraction of chlorophyll. It was discovered at the A.D Laboratory that scopolamine could be completely extracted by a simple percolation with water. Addition of acid produced no better results and promoted a hydrolysis to scopino-l-tropic acid. During the extraction the temperature had to be kept low in order to avoid the undesirable racemization to optically inactive atropine components which would affect the physiological action of the product.
- 2) The scopolamine base obtained in this water-percolation extraction was dissolved in an equal amount of absolute alcohol. The required amount of freshly prepared alcoholic hydrogen bromide was added, followed by addition of pure acetone until clouding occurred. This cloudiness was removed by addition of absolute alcohol, and the solution seeded with a crystal of the desired product to initiate crystallization. The mixture was allowed to stand in the ice box for three days to complete the crystallization, after which the product was removed by filtration, washed with acetone and dissolved in 90 percent of its weight of distilled water. Charcoal was added to decolorize the solution. The mixture was filtered into flat dishes and seeded with a crystal of the pure product. The dishes were allowed to stand for two days in the ice box during which time complete precipitation occurred. The precipitate was filtered and dried on clay plates at 100°C. Extra crystals could be obtained from the mother liquor by a similar treatment. Finally, residual scopolamine was obtained by adding sodium bicarbonate to the mother liquor. This scopolamine was re-worked in the above fashion to improve the yield.

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Comment:

1. The plant at Reichenberg/Hierderlausitz had been a branch factory of the former Schering A.G.

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